

## REMARKS

Claims 1-4, 8-11 and 61-62 are pending in this application. No claim amendments are made in this paper, and thus, no new matter has been added.

### **I. The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn**

On page 4 of the Office Action, claims 1-11, 8-11, and 61-62 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Marx *et al.* Proc. Am. Soc. Clin. Oncology (1997), Vol. 18, No. 1751, page 454a (hereafter “Marx”) and Houghton *et al.* Cancer Chemother. Pharmacol. (1995), Vol. 36, page 393 (hereafter “Houghton”). In particular, it is alleged, based on *Ex parte Quadranti*, 25 U.S.P.Q.2d 1071 (Bd. Pat. Appl. & Inter. 1992), that combining thalidomide, as disclosed in Marx, and topotecan, as disclosed in Houghton, would have been obvious. Applicants respectfully traverse this rejection.

The U.S. Supreme Court has recently addressed the test for obviousness under 35 U.S.C. § 103. (*KSR International Co. v. Teleflex Inc.* 127 S.Ct. 1727, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385 (2007)). In *KSR*, the Supreme Court rejected the Federal Circuit’s rigid application of the “teaching, suggestion, motivation” test (“the TSM test”) in determining obviousness in the particular case in question. (*Id.* at 1739 (emphasis added)). According to the Supreme Court, the correct standard to apply is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). (*Id.* at 1734). However, the *KSR* decision indicated while the TSM test is not the sole method for determining obviousness, it may still be a factor. (*Id.* at 1741 (“When it first established [the TSM test], the Court...captured a helpful insight.”)). Indeed, on May 3, 2007, the Deputy Commissioner of Patents circulated a memorandum (“USPTO Memorandum”) to the Technology Center directors pointing out that the TSM test was not completely abolished in *KSR*.

The *Graham* factual inquiries, which establish a guide for determining obviousness, are: (1) determining the scope and contents of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating any evidence of secondary considerations. (*KSR*, 127 S.Ct. at 1734 (citing *Graham*, 383 U.S. at 15-17)).

Applicants respectfully submit that, on the basis of *KSR* and *Graham*, the instant claims are not obvious over Marx and Houghton in combination. Specifically, Applicants respectfully submit that: (1) on the basis of the scope and contents of the prior art, it would

not have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Marx and Houghton; and (2) sufficient unexpected results are provided to rebut any presumption of obviousness.

**A. On the basis of the scope and contents of the prior art, it would not have been obvious to one of ordinary skill in the art to combine the teachings of Marx and Houghton.**

The Examiner has rejected the pending claims as allegedly unpatentable over Marx and Houghton in combination because “the use of materials in combination, each of which is known to function for intended purpose, is *prima facie* obvious.” (Office Action, page 4).<sup>1</sup> In this regard, the Examiner relies on the alleged precedent set forth in *Ex parte Quadranti*, 25 U.S.P.Q.2d 1071 (Bd. Pat. Appl. & Inter. 1992).

Applicants respectfully submit that the Examiner is improperly applying *Ex parte Quadranti* to the present invention.

To begin, the test for obviousness is not a rigid approach, such as the one taken by the Examiner in the Office Action. As the Examiner is aware, *KSR* is now the controlling authority with regard to determinations of obviousness under 35 U.S.C. §103. (*KSR*, 127 S.Ct. at 1727). In this regard, the Supreme Court in *KSR* expressly warned against the application of “rigid and mandatory formulas” in determining obviousness. (*Id* at 1741).

Instead, the applicability of *Ex parte Quadranti* is dependent upon the facts of each particular case, and care must be taken by the Examiner to not apply the case rigidly and broadly. As the Federal Circuit has made it clear, “[a]lthough a reference need not expressly teach that the disclosure contained therein should be combined with another...the showing of combinability, in whatever form, must nevertheless be clear and particular.” (*Winner International Royalty Corp v. Wang*, 202 F.3d 1340, 1348-49, 53 U.S.P.Q.2d 1580 (Fed. Cir. 2000)(emphasis added)).

Indeed, the Supreme Court, in *KSR* itself, clearly held that the allegation of *prima facie* obviousness set forth by the Examiner in the Office Action is based on a mistaken

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<sup>1</sup> Applicants respectfully point out that in stating “the use of materials in combination, each of which is known to function for intended purpose, is *prima facie* obvious”, the Examiner has stated the rule from *Ex parte Quadranti* too broadly. (Office Action, page 4) (emphasis added). Indeed, the Court in *Ex parte Quadranti* instead stated: “It is generally true that the use of materials in combination each of which is known to function for the intended purpose is *prima facie* obvious.” 25 U.S.P.Q.2d at 1072 (emphasis added). However, it is well settled that combining two pharmaceutical agents is not generally *prima facie* obvious in view of various decisions by the Federal Circuit, as discussed below.

interpretation of legal principles. This is because “[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” (*KSR*, 127 S.Ct. at 1741 (*quoting In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006))). In this regard, the *KSR* Court explained:

[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art... This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known. (*Id.*)

Consequently, Applicants respectfully point out that the rejection based on Marx and Houghton, *i.e.* based merely on the fact that thalidomide and topotecan were independently known in the prior art, is flatly contrary to the well-established legal principles<sup>2</sup>.

Furthermore, Applicants respectfully submit that indeed there would have been no reason for those skilled in the art to combine Marx and Houghton. As pointed out in Applicants’ previous responses, thalidomide was not an approved anti-cancer drug at the time of the invention. What is more, because the administration of thalidomide to pregnant women was known to cause birth defects, the sale of thalidomide has been strictly controlled. (Specification, page 6, line 38 – page 7, lines 1-5). Therefore, there existed better alternatives to thalidomide, and thus a person of ordinary skill in the art would not have been prompted to select thalidomide to use in combination with a topoisomerase inhibitor. In this regard, Applicants respectfully invite the Examiner’s attention to *Yamanouchi*, 231 F.3d 1339, a copy of which is attached hereto as Exhibit A. In *Yamanouchi*, the Court held that the selection of a compound for use in a combination was not obvious even though the compound exhibited activity that was three times greater than the benchmark. (*Id.* at 1345 (emphasis added)). The Court explained that the required motivation to use the compound was not shown in light of better alternatives that were up to ten times more active than the benchmark, stating that “other more active compounds would have been the obvious choices.” (*Id.* at 1345).

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<sup>2</sup> In a case decided following *KSR*, the Federal Circuit once again emphasized “the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination.” (*Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, --- F.3d.---, 2007 WL 1839698 (C.A. Fed. (N.Y.)), 83 U.S.P.Q.2d 1169).  
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Like in *Yamanouchi*, there were better alternatives to thalidomide available at the time of this application in view of the facts that thalidomide was not approved and that thalidomide's side effects were well known at that time. Therefore, Applicants respectfully submit that no reason to combine Marx and Houghton would have existed.

In sum, at the time of the invention, one of ordinary skill in the art would not have been prompted to combine Marx and Houghton, and thus, no *prima facie* case of obviousness is established by those references. Consequently, Applicants respectfully request that the rejection be withdrawn for this reason alone. Furthermore, even assuming, *arguendo*, that a *prima facie* case of obviousness were established by Marx and Houghton, Applicants respectfully submit that any presumption of obviousness should be rebutted in view of the superior results provided herein, as discussed below.

**B. Sufficient unexpected results are provided to rebut any presumption of obviousness.**

It is alleged in the Office Action that “[i]n the absence of some proof of a secondary nature or of some specific limitations which would tip the scale of patentability in the favor of the instantly claimed invention, it would have been obvious to one of ordinary skill in this art at the time of the invention to co-administer two components (thalidomide and topotecan)...” (Office Action. Page 5).

Applicants respectfully submit that the “proof of a secondary nature” has been provided in the specification. Specifically, the specification provides that “the combined use of a topoisomerase inhibitor and thalidomide to a patient suffering from cancer provides a unique and unexpected synergism.” (Specification, page 14, lines 29-31). In this regard, Applicants provided, as evidence, a copy of *BioWorld Today*, November 4, 2005, page 2 (hereafter “Bioworld article”), which reports that the combination of thalidomide and topotecan has an improved efficacy and safety in the treatment of epithelial ovarian cancer as compared with topotecan alone. Applicants reiterate that this article alone would be sufficient to rebut any presumption of obviousness.

Be that as it may, Applicants now additionally submit herewith an article from the National Cancer Institute which describes a recent report from the 37<sup>th</sup> Annual Meeting of the Society of Gynecologic Oncologists (hereafter “Report”).<sup>3</sup> According to this article, “[a]dding thalidomide to a topotecan regimen for recurrent ovarian cancer significantly

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<sup>3</sup> Available at <http://ctep.cancer.gov/resources/gcig/news032406.html>, attached as Exhibit B for the Examiner's convenience.

enhances therapeutic response and increases progression-free survival without increasing incidence of toxicity.” (*Id*). The article reports that “47% of 30 patients who received thalidomide plus topotecan experienced a complete or partial response, significantly more than the 21% of 39 patients who received topotecan alone.” (*Id*).

Thus, this additional evidence clearly demonstrates the synergistic effects of topotecan and thalidomide. In view of the superior synergistic effects documented in the Bioworld article and the Report, Applicants respectfully point out that the pending claims are unobvious, and thus, request that the rejection be withdrawn.

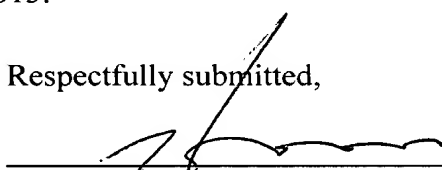
## **II. Conclusion**

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are allowable, and thus, request that the rejections be withdrawn.

No fee is believed due for the submission of this paper. However, if any fees are due for the submission of this paper or to avoid abandonment of this application, please charge them to Deposit Account No. 50-3013.

Respectfully submitted,

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